REMARKS

Status of the Claims

Claims 25-29, 43, and 45-47 are pending and claims 43 and 45-47 are under consideration in this application, claims 25-29 having been withdrawn for allegedly being drawn to separate inventions.

No amendments are made herein. Thus, after entry of the present Response, claims 25-29, 43, and 45-47 will still be pending and claims 43 and 45-47 will still be under consideration in this application.

Telephone Interview

Applicants thank the Examiner and Examiner Janet Andres for their courtesy in the telephone interview with Applicants' undersigned representative on May 8, 2007. The Examiner indicated in the interview that, because he had only very recently been assigned to the instant application and had not had time to review the references cited in the Office Action of May 2, 2006, he was not able to comment on the arguments recited by Applicants' undersigned representative during the interview and that Applicants should include the comments made during the interview in a written response. Applicants would like to request another interview with the Examiner and Examiner Andres after the Examiner has had an opportunity to review the cited references.

35 U.S.C. § 103(a) rejection

Claims 43 and 45-47 stand rejected as allegedly being unpatentable over Kamata et al., Johnson et al. (U.S. Patent No. 5,851,786; the "'786 patent"), Varon et al., Mobley et al. (U.S. Patent No. 5,134,121; the "'121 patent"), Mattson et al., Olson et al., 1994 ("Olson et al. (a)"), and Olson et al. 1993 ("Olson et al. (b)"). Applicants respectfully traverse the rejection.

From the comments on page 2, line 25, to page 10, line 6, of the Office Action, Applicants understand the Examiner's position to be that it would have been obvious to one of

ordinary skill in the art to combine the disclosures of the cited references and hence to practice the methods of present claims. Applicants respectfully disagree with this position.

Firstly, only two of the cited references (Kamata et al. and the '786 patent) even mention C3 ADP-ribosyl transferase (CART). Both only disclose the use of CART as a tool in *in vitro* basic biological experiments designed to study Rho family members and proteins that interact with them. There is not the least suggestion in either reference of using CART in any clinical setting, let alone in the methods of the present claims.

Kamata et al. describes experiments with malignant GOTO cells that lead the authors to suggest, with significant reservation, that CART might be a neurotropic differentiative factor for such cells (see, e.g., the Abstract, lines 10-12, and page 427, column 1, lines 10-15). There no suggestion that it might be involved in axonal regeneration at all and particularly in normal (as opposed to malignant) cells. More importantly even, there is also not the least suggestion of any clinical applicability of CART, let alone of using it (or a functional fragment of it) during surgery for the repair of traumatic spinal cord injuries as in the instant claims. Indeed there is teaching in the article that would very likely dissuade one of ordinary skill in the art from even looking into the possibility. Thus, the article indicates that very high doses of CART were required for the effect observed on the GOTO cells and that this was because only a very small fraction of the CART to which the cells were exposed actually got into the cells (see, e.g., page 427, column 1, lines 11-48). Moreover, Kamata et al. cites three references as showing that CART induces "dysfunctional" changes in the cytoskeleton of cultured cells (see, e.g., page 427, column 2, lines 23-25).

Thus, the reference contains no incentive that would motivate one of ordinary skill in the art to combine its mention of CART with the teachings of any of the other cited references that might mention clinical treatment (e.g., repair of traumatic spinal cord injuries) and hence to use CART in such clinical applications. Indeed, it contains disclosure that would probably actively dissuade such an artisan from doing so.

The other reference that mentions CART, the '786 patent, describes methods for identifying compounds capable of regulating actin polymerization, stress fiber formation, and/or

focal adhesion assembly and methods to treat or control certain diseases and conditions with such compounds. The only mention of CART in the '786 patent is as an experimental tool to probe the relationships in Swiss 3T3 embryonic fibroblast cells between Rho proteins and the $G_{\alpha 12}$ and $G_{\alpha 13}$ signal transduction G proteins (see Example 3). From these experiments the inventors concluded that $G_{\alpha 12}$ and $G_{\alpha 13}$ regulate Rho-dependent actin polymerization resulting in stress fiber formation and assembly of focal adhesions and therefore integrate heterotrimeric G protein-coupled receptors with regulation of Rho (see, e.g., column 22, lines 39-43). However, in Example 3 (where these experiments are described in the '786 patent) there is no disclosure, or even the least suggestion, of using CART, or a functional fragment thereof, for any clinical treatment, let alone in the methods of the present claims. For example, there is no teaching of whether CART would act the same in nerve cells as in 3T3 embryonic fibroblasts (i.e., to induce Rho-dependent stress fiber formation) and, even if it did, whether induction of stress fiber formation would result in axonal regeneration in damaged axons.

In addition, among the list of compounds that the '786 patent does indicate can be used in its screening tests and methods of treatment, there is not the least suggestion of using molecules such as CART, or molecules even related to it. The focus in the '786 patent is on compounds with structures based on the structures of G or Rho proteins. It teaches that appropriate compounds can be modified intracellular signal transduction molecules, i.e., compounds capable of regulating the activity of a subunit of a G protein (see, e.g., column 10, lines 38-45) . Thus, appropriate compounds would be, for example, one capable of interfering with the association of a subunit of a G protein with a Rho regulatory molecule, e.g., a compound having similar structure to a Rho regulatory molecule binding site on a G protein or one having similar structure to a G protein binding site on Rho regulatory molecule (see, e.g., column 10, lines 45-54). Other appropriate compounds taught by the '786 patent are mutants of receptors that are coupled to G proteins, e.g., compounds having similar structures to ligands for such receptors (see, e.g., column 11, lines 6-14). There is no teaching or the least suggestion in the reference that CART falls into any of the above categories of molecules that are useful for its screening assays and methods of treatment.

For the above reasons alone, the '786 patent, like Kamata et al., would provide not the least motivation to one of ordinary skill in the art to combine its mention of CART with the disclosure of any clinical procedure, let alone one involving repair of damaged spinal cord axons, that might be mentioned in the other cited references and hence to practice the methods of the instant claims. Indeed, the '786 patent contains additional disclosure that, also like Kamata et al., would actually provide a disincentive to such an artisan to do so. Thus, as pointed out in the Responses filed June 2, 2004, and January 1, 2006, the object of the treatment methods disclosed by the '786 patent is to "regulate cellular function" (column 2, line 24) and the methods are, in particular, "useful for preventing or treating diseases involving abnormal growth or the migration of cells from one location in an animal to another." (column 17, lines 23-25). It is thus clear that the treatment methods of the '786 patent are directed at inhibiting unwanted cellular activity (e.g., cell growth) in a variety of diseases. On the other hand, the present claims are directed at enhancing a cellular activity (i.e., neuronal axon growth) in order to repair traumatic damage to spinal cord axons. While the '786 patent does refer to treating two nervous system diseases (Parkinson's and Alzheimer's diseases; column 17, line 34), it is clear (from the above cited text) that the inventors contemplated doing so by inhibiting undesirable cellular responses in these diseases rather than by enhancing neuronal axon growth as the present claims require in order to repair traumatic spinal cord injury. Thus, not only does '786 patent provide no suggestion or motivation to use CART in any clinical application, it provides a disincentive to using for repair of any traumatic nervous system (including spinal cord) injuries even the compounds it does disclose as being useful for therapeutic purposes (see above).

The other references cited in the Office Action contain no mention of CART but describe work with various mammalian endogenous factors (most notably nerve growth factor (NGF)) that operate by an entirely different mechanism from exogenous (bacterial) CART.

Thus, Varon et al. is a review article that describes, among other procedures, one for spinal cord repair in which NGF is used to supplement the repair by a bridge (consisting of nerve tissue) between the ends of transected spinal cord. However, the reference contains no mention or even the least suggestion of CART, or indeed of Rho or G proteins, in any context, let alone as

an agent for repair of a damaged spinal cord. Thus, the reference contains no motivation to those skilled in the art to combine its disclosure of spinal cord repair with the mention of CART in either Kamata et al. or the '786 patent and hence to use CART, or a functional fragment thereof, in the methods of the instant claims.

The '121 patent describes NGF factor peptides that can act as NGF agonists or antagonists. Mattson et al. describes the use of endogenous growth factors (e.g., IGF, FGF, and NGF) that protect neurons against excitotoxic or ischaemic damage by stabilizing homeostasis. The Olson references describe the use of some of the same and other growth factors (e.g., PDGF, TGF, and CNTF) for neural regeneration. In none of the '121 patent, Mattson et al., and the Olson references is there any disclosure or the most minimal suggestion of treating during surgery a traumatic spinal cord injury with NGF or anything else. Moreover, as in Varon et al., not only is there no mention in these references or a minimal suggestion of CART in any context, there is also no mention or suggestions of Rho or G proteins. In light of the above considerations, none the '121 patent, Mattson et al., and the Olson references contain the least motivation to combine the disclosures of two or more of the references and hence to use CART, or a functional fragment thereof, in the methods of the instant claims.

Even if one of ordinary skill in the art had hypothetically been motivated to combine the disclosures of two or more of the cited references and hence to practice the methods of the instant claims (which, for the reasons given above, he or she would clearly not have), in light of the dearth of teaching in the art on the clinical applicability of CART, he or she would have no reasonable expectation of success.

Finally, given the lack of such teachings in the prior art, the results of *in vivo* experiments showing dramatic axonal growth in response to CART in a rat central nervous system (crushed optic nerve) model described in Example II of the instant application constitute, at the very least, surprising and unexpected results.

Applicants provide the following remarks in response to specific comments made in the Office Action.

In response to the comments on page 7, lines 14-17, and page 9, lines 4-7, of the Office Action, Applicants submit that: (a) the relevant statements in the Amendment and Response of January 12, 2006, were made mainly in order to point out that the reference lacked the motivation to combine its disclosure with any of the other cited references and not in the belief that Kamata et al. should disclose each and every element of the claims at issue in order for an obviousness rejection to be made; and (b) as argued above, while the authors do suggest with some hesitation that CART may be involved in the *in vitro* differentiation of malignant GOTO neuroblastoma cells, they neither disclose or even remotely suggest that it may be useful in any clinical application, let alone in regenerating the axons of traumatically injured normal spinal cord nerve cells. Moreover, the article provides teachings that would dissuade one ordinarily skilled in the art from using it for any clinical neurological applications.

In response to the comments on page 7, line 22, to page 9, line 2, of the Office Action, Applicants respectfully submit that the recitation on page 8 to page 9 of the Amendment and Response filed January 12, 2006, of the differences between the conditions the '786 patent states to be treatable by its methods and the condition (i.e., traumatic injury to spinal cord) that is treated in the methods of the instant claims was provided to point out one aspect of the failure of the '786 patent to provide the requisite motivation to combine its disclosure with that of one or more of the other cited references (see additional arguments in support of this position above). Applicants respectfully submit that, as pointed out above and contrary to the statement on page 8, lines 2-4, of the Office Action, the '786 patent does not teach "administration of C3ART to the patient populations exhibiting neurological/neurodegenerative disorder."

In regard to the disclosure of the '786 patent, Applicants are not sure where the quotation on page 8, line 10, to page 9, line 1, of the Office Action comes from. This Office Action appears to indicate that it comes from the '786 patent but Applicants have been unable to find the relevant text in the '786 patent.

With respect to the comments in the Office Action in regard to the Varon et al. reference (Office Action, page 7, lines 18-21 and page 9, lines 9-10), as pointed out above, while the reference describes the use of NGF to supplement treatment with nerve tissue bridge of a

transected spinal cord, it contains no motivation whatsoever to combine its disclosure with Kamata et al. and/or the '786 patent. Moreover, also as described above, even if it did contain such motivation, because Kamata et al. and the '786 patent do not describe or even suggest any clinical application of CART at all, let alone treating a traumatic spinal cord injury, such an artisan would not consider using CART, or a functional fragment of it, in the methods of the instant claims. Indeed, even if such an artisan did hypothetically for a moment consider such a possibility, in light of the above-described disincentives in Kamata et al. and the '786 patent, he or she would have been dissuaded from doing so.

With respect to the comments on page 9, line 10, to page 10, line 2, of the Office Action, as pointed out above, none of the '121 patent, Mattson et al., and the Olson et al. references describe any pathologic condition specifically of spinal cords, let alone traumatic injuries to spinal cord. Moreover, also as pointed out above, none of these references contain disclosure that would motivate one ordinarily skilled in the art to combine its disclosure with that of Kamata et al and/or the '786 patent. However, even if any of these secondary references did hypothetically provide such motivation, because Kamata et al. and the '786 patent do not describe or even suggest any clinical application of CART at all, let alone treating a traumatic spinal cord injury, and indeed contain disclosure that would discourage one of ordinary skill in the art from using to regenerate any damaged nerves (including spinal cords), such an artisan would not consider using CART, or a functional fragment of it, in the methods of the instant claims.

With respect to the comments on page 10, lines 2-6, of the Office Action, in light of the above-described disclosure of the cited references, Applicants respectfully submit that the prior art could in no way predict the success of using CART to treat traumatic injuries to the CNS as in the *in vivo* experiment described in Example II. Moreover, with respect to the statement on page 10, line 5, of the Office Action, in that Applicants are unaware of any prior description of the use of CART for the treatment of any neurological condition prior to the experiments disclosed for the first time in the present application, no useful comparison is available.

In view of the above considerations, Applicants respectfully submit that a person of ordinary skill in the art (such a person having common sense) would not have been motivated by one or more of the cited references to practice the methods of the instant claims. Thus, the claims cannot be considered obvious over the cited art. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the claims under consideration patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the claims under consideration to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time. Please charge the fee for the extension of time and any other fees or make any credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 12552-002001.

Respectfully submitted,

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